REMARKS

Claims 1-21 are pending in the present application. By virtue of this response, claims 1, 2, 9, 18, and 20 have been amended; claims 14-17 and 21 have been canceled; and new claims 22-25 have been added. Support for amendment of claim 1 is found in the specification, *inter alia*, on page 5, paragraph **[0013]**; and on page 6, paragraph **[0017]**. Support for new claim 22 is found in original claim 1. Support for new claim 23 is found in the specification, *inter alia*, on page 22, paragraph **[0090]**. Support for new claims 24 and 25 is found in the specification, *inter alia*, on pages 21-22, paragraph **[0090]**.

With respect to all amendments and canceled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional application.

Priority

The Examiner states that the provisional application (Ser. No. 60/486,865) fails to provide adequate support under 35 U.S.C. §112 for claims 1-21 of the present application.

Although Applicants disagree with the Examiner, Applicants have amended claim 1 to delete the recitation that the method is "without chromatographic separation" and "assessing the Hcy co-substrate conversion product SAH generated in step (a)." Applicants respectfully submit that claim 1 as amended is supported by the provisional application; and thus, the priority claim for the present application is proper.

The Examiner also states that claim 8 is not disclosed in the provisional application.

Applicants respectfully disagree and point out that support of the presently pending claim 8 can be found in the provisional application, *inter alia*, in paragraph **[0019]** of the provisional application.

The Examiner further states that claims 19 and 20 are not disclosed in the provisional application.

Applicants respectfully disagree and point out that support of the presently pending claims 19 and 20 can be found in the provisional application, *inter alia*, in paragraph **[0030]** of the provisional application.

Claim rejections under 35 U.S.C. §112, second paragraph

Claims 1-21 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The Examiner states that claim 1 is rendered indefinite by the phrases "**assessing** the Hcy co-substrate conversion product SAH..." and "... adenosine (Ado), which is **assessed** to determine the presence, absence and/or amount..." The Examiner further states that it is not clear what features of SAH and Ado are assessed since no indication is given as to how the assessment of SAH relates to assaying homocysteine (Hcy), and since the claim states that Ado is assessed to determine the presence, absence and/or amount of Hcy in the sample. Additionally, the Examiner states that it is not clear what qualities of the assessed Ado feature would indicate the presence, absence and/or amount of the Hcy in the sample, as no criteria is given.

Applicants respectfully traverse this rejection.

Applicants note that the specification provides that the term "assessing" includes quantitative and qualitative determination in the sense of obtaining an absolute value for the amount or concentration of the analyte, and also of obtaining an index, ratio, percentage, visual or other value indicative of the level of analyte in the sample. The term "assessing" means determining an absolute and/or a relative value (including quantitative and qualitative) for the analyte, and thus, the term is clear to one skilled in the art.

Applicants also note that one skilled in the art knows how to determine the correlation between the presence or absence and the concentration of Hcy in a sample and the presence or absence and the concentration of the Ado generated in the reaction system based on the reaction system shown in Figure 1 of the present application. Hcy samples with known Hcy concentrations may be used to generate the correlation for an assay system. An example of such correlation is shown in Figure 2 of the present application. Thus, claim 1 is clear to one skilled in the art, and no specific criteria needs to be recited in the claim.

In view of the above, Applicants respectfully request that the rejection be withdrawn.

The Examiner rejects claims 1 because it recites "... containing the SAH with a SAH hydrolase to generate Hcy from **SAM**..."; and the Examiner suggests to replace the term "SAM" with "SAH". The Examiner further states that it is not clear whether Hcy or SAM (replaced with SAH for examination purpose) is cycled into the Hcy conversion reaction.

Applicants respectfully note that claim 1 has been amended to delete the term "from SAM", and to clarify that Hcy is cycled into the Hcy conversion reaction. Applicants respectfully request that the rejection be withdrawn.

The Examiner states that claim 2 is indefinite because it is not clear what role the recited step has in assessing the Ado or in accomplishing the method for assaying Hcy.

Applicants respectfully note that claim 2 has been amended to recite that "the Ado is assessed by contacting the Ado with an adenosine converting enzyme other than the SAH hydrolase." As discussed above, the presence, absence, and/or amount of the Ado can be used for determining the presence, absence, and/or amount of Hcy. Thus, claim 2 as amended is definite. Applicants respectfully request that the rejection be withdrawn.

The Examiner states that claim 3 is indefinite because it is not clear what features of what features of Ado, the co-substrate, or the reaction product, are assessed. The Examiner further

states that no criteria is given as to how the assessment of the Ado is effected by the assessment of the co-substrate or the reaction product.

Applicants respectfully traverse this rejection. As discussed above, the term "assessing" is clear to one skilled in the art and is defined in the specification to mean determining an absolute and/or a relative value (including quantitative and qualitative) for the analyte. As discussed above, one skilled in the art knows how to establish specific correlations for the analytes based on an enzymatic reaction. Indeed, Diazyme's Enzymatic Homocysteine Test Kit based on the presently claimed invention has been approved by FDA (*See* Exhibit 2). Thus, claim 3 is definite. Applicants respectfully request that the rejection be withdraw.

The Examiner states that claim 9 is rendered indefinite by the term, "the blood sample", since it lacks antecedent basis. Although Applicants disagree with the Examiner, claim 9 is amended to delete the term "sample". Applicants respectfully request that the rejection be withdrawn.

The Examiner states that claim 14 is rendered indefinite by the phrase "**assessing** the Hcy co-substrate conversion product SAH...", as it is unclear what feature of SAH is assessed; and no criteria is given as to what characteristics of the assessed feature would indicate the presence, absence and/or amount of the Hcy in the sample. Applicants note that claims 14-17 are canceled. Accordingly, the rejection is moot. Applicants respectfully request that the rejection be withdrawn.

The Examiner states that claims 18 and 21 are rendered indefinite by the phrase "S-adenosylmethionine (SAM) or ATP, Met and a SAM synthase", as it is written it could be interpreted as one of the following: (i) (SAM or ATP) and Met and a SAM synthase, (ii) SAM or (ATP and Met and a SAM synthase). The Examiner further states that in view of claims 12, 13, 16, and 17, the phrase will be interpreted as option (ii). The Examiner states that claims 18 and 21 are indefinite because it is not clear what is defined by "a reagent for assessing" adenosine (Ado) or SAH, and what feature of Ado or SAH is assessed, thus it is unclear what reagents accomplish the assessment.

Applicants note that claim 18 is amended and claim 21 is canceled. Applicants respectfully submit that the feature to be assessed is clear to one skilled in the art as discussed above; and reagents that can be used for assessing Ado and SAH are well known in the art are described in the specification. For example, Ado may be assessed by monitoring the reaction with enzymes which convert it directly or indirectly to products which may be detected photometrically. Suitable enzymes include adenosine deaminase (which converts adenosine to inosine) and adenosine kinase (which converts adenosine and ATP to ADP and phosphorylated adenosine). *See* page 16, paragraph **[0065]**. In view of the above, Applicants respectfully submit that claim 18 is definite, and request that the rejection be withdrawn.

The Examiner states that claim 20 is rendered indefinite by the term "the adenosine converting enzyme", since it lacks antecedent basis. Applicants respectfully note that claim 20 is amended to depend from claim 19, which provides antecedent basis for the term "the adenosine converting enzyme". Applicants respectfully request that the rejection be withdrawn.

In view of the above, Applicants respectfully request that the rejections under 35 U.S.C. §112, second paragraph be withdrawn.

Claim rejections under 35 U.S.C. §103(a)

A. Rejection over Matsuyama et al. (US 2002/0123088) in view of Sundrehagen (US 5,958,717)

Claims 14-16 and 18-21 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Matsuyama et al. (US 2002/0123088 A1) in view of Sundrehagen (US 5,958,717). The Examiner states that Matsuyama et al. teach a method for determining the presence, absence, and/or amount of homocysteine (Hcy) in a sample wherein Hcy is first reduced, then reacted with a homocysteine-converting enzyme and a homocysteine co-substrate; and when homocysteine methyltransferase is used as the Hcy-converting enzyme, the enzyme produces L-Met and SAH, where Hcy and SAM serve as the substrates. The Examiner further states that Matsuyama et al. do not expressly disclose assessing the produced SAH of the above reaction

(catalyzed by SAM-dependent homocysteine S-methyltransferase) in order to determine the presence, absence and/or amount of Hcy in a sample. The Examiner also states that Matsuyama et al. teach a kit comprising SAM-dependent homocysteine S-methyltransferase and SAM, since the enzyme and substrate are together in a solution. With respect to Sundrehagen reference, the Examiner states that Sundrehagen discloses a method for assaying Hcy in a sample without chromatographic separation wherein the sample is contacted with SAH hydrolase, followed by the step of "assessing (preferably photometrically) a non-labelled analyte selected from the homocysteine co-substrate and the products of the enzymatic conversion of homocysteine by said enzyme". The Examiner further states that according to claim 3 of Sundrehagen, when SAH hydrolase is used, the analyte that is assessed is SAH; and assessment occurs by assessing adenosine (Ado). The Examiner further states that Sundrehagen teaches a kit for performing the method that comprises SAH hydrolase and an adenosine converting enzyme, such as adenosine kinase. The Examiner concludes that at the time the invention was made, it would have been obvious to a person of ordinary skill in the art to have modified the Matsuyama invention such that the presence of SAH is assessed instead of Met, by using the methods disclosed in Matsuyama et al. and Sundrehagen; and the resulting reaction solution would have formed a kit comprising SAM-dependent homocysteine S-methyltransferase, SAM, SAH hydrolase, and an adenosine converting enzyme.

Without acquiescence to the rejection and in the interest of expediting prosecution, Applicants note that claims 14-16 and 21 have been canceled. Thus, rejection as applied to these claims is rendered moot.

Applicants respectfully traverse the rejection to claims 18-20. Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three criteria must be met. First, there must be some suggestion, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. These requirements are summarized in the MPEP (MPEP §2143, and §2143.01 to §2143.03), and are based on well-settled case law: *In re Fine*, 837

F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); and *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

Applicants respectfully submit that the cited references do not provide the motivation to combine reference teachings. Claim 18 as amended recites a kit for assaying Hcy in a sample, which kit comprises: a) a S-adenosylmethionine (SAM)- dependent homocysteine S-methyltransferase; b) S-adenosylmethionine (SAM); or ATP, Met and a SAM synthase; c) a SAH hydrolase; and d) a reagent for assessing adenosine (Ado). As acknowledged by the Examiner, Matsuyama et al. do not teach or suggest assessing the produced SAH of the SAM-dependent homocysteine S-methyltransferase catalyzed reaction. Although Matsuyama et al. note the difficulty of determining L-methionine and propose to detect D-methionine for assaying Hcy, Matsuyama et al. do not provide any suggestion to assay the SAH. Sundrehagen does not teach or suggest using SAH hydrolase to detect SAH. Sundrehagen discloses reacting Ado with Hcy in a sample in the presence of SAH hydrolase to form SAH, and then assessing the change of Ado or SAH for assaying Hcy in a sample. Thus, SAH hydrolase is used as Hcy converting enzyme, not as a method for assessing SAH. *See* Sundrehagen, col. 3, lines 1-5. Since there is no teaching or suggestion in Matsuyama et al. to include any reagents for assaying SAH, and no teaching or suggestion for assaying SAH using SAH hydrolase, one skilled in the art would not be motivated to combine the kit in Matsuyama et al. with the kit in Sundrehagen for assaying Hcy. Thus, the Examiner has not set forth a *prima facie* case for obviousness for claims 18-20.

In view of the above, Applicants respectfully request the rejection be withdrawn.

B. Rejection over Matsuyama et al. and Sundrehagen, further in view of Suzuki et al. (US 4,981,801) or Kawaski et al. (US 2003/0138872)

Claims 1-8, 10-12, 14-16, and 18-21 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Matsuyama et al. and Sundrehagen as applied to claims 14-16 and 18-21 above, and further in view of Suzuki et al. (US 4,981,801) or Kawasaki et al. (US 2003/0138872

A1). The Examiner states that Matsuyama et al. and Sundrehagen do not expressly disclose cycling the Hcy generated from the reaction catalyzed by SAH hydrolase into the Hcy conversion reaction by the SAM-dependent homocysteine S-methyltransferase. The Examiner further states that Suzuki et al. disclose that enzymatic cycling permits the analysis of a very small amount of a substance in a sample, and in the enzymatic cycling method, a substance is measured in a multiplying manner by combining two enzyme reactions. The Examiner states that Kawasaki et al. disclose a method involving enzymatic cycling for assessing the amount of homocysteine in solutions such as blood and urine, and the enzymatic cycling assay taught by Kawasaki involves converting homocysteine to cystathionine by the enzyme CBS, and converting cystathionine to homocysteine by enzyme CBL.

Applicants respectfully note that claims 14-16 and 21 have been canceled. Thus, rejection as applied to these claims is rendered moot.

Applicants respectfully traverse the rejection to claims 1-8, 10-12, and 18-20. Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness of claims 1-8, 10-12, and 18-20. Applicants respectfully submit that the cited references do not provide the motivation to combine reference teachings. As acknowledged by the Examiner, neither Matsuyama et al. nor Sundrehagen teach or suggest cycling the Hcy generated from combining two enzymatic reactions shown in Figure 1 of the present application for cycling the Hcy from the reaction catalyzed by SAH hydrolase into the Hcy conversion reaction catalyzed by the SAM-dependent homocysteine S-methyltransferase. Although Suzuki et al. and Kawasaki et al. disclose using enzymatic cycling system for assaying a substance in a sample or Hcy in a sample, neither of the references teach or suggest combining the two enzymatic reactions to form a cycling reaction system as recited in claim 1. One of ordinary skilled in the art would not motivated to combine the teachings of Matsuyama et al. with Sundrehagen, Suzuki et al., or Kawasaki et al.

In addition, the cited references do not render claims 1-8, 10-12, and 18-20 obvious because, even assuming, *arguendo*, the combination of the references is permitted, combination of the cited references does not teach all elements of the presently claimed invention. For example,

claim 1 recites "contacting the SAH generated in step (a) with a SAH hydrolase to generate Hcy, which is cycled into the Hcy conversion reaction by the SAM-dependent homocysteine S-methyltransferase to form a Hcy co-substrate based enzyme cycling reaction system." As acknowledged by the Examiner, Matsuyama et al. and Sundrehagen do not teach any enzymatic cycling at all. Suzuki et al. teach an enzymatic cycling generally but has no teaching on homocysteine assay at all. Kawasaki et al. teach an enzymatic cycling in a homocysteine assay but the cycle taught in Kawasaki et al. is totally different from the enzymatic cycling recited in the present claim 1. Therefore, the combination of the cited references does not teach enzymatic cycling recited in the present claim 1. Similarly, the combination of the cited references does not teach the combination of the enzymes and other reagents as recited in claim 18. Thus, the Examiner has not set forth a *prima facie* case for obviousness for claims 1-8, 10-12, and 18-20.

Further, evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. MPEP § 716.01(a)II. "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness. *Id. citing In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987). " No set number of examples of superiority is required. *Id.* Similarly, presence of a property not possessed by the prior art is evidence of nonobviousness. MPEP § 716.01(a)II. *citing In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (rejection of claims to compound structurally similar to the prior art compound was reversed because claimed compound unexpectedly possessed anti-inflammatory properties not possessed by the prior art compound).

While the applicants do not believe that the Examiner has established a *prima facie* case that the claimed invention would have been obvious, YUAN 132 Declaration shows that the claimed invention is not obvious. YUAN 132 Declaration demonstrates that the claimed invention provides unexpected technical advantages over the Kawasaki assay in at least two regards. First, the presently claimed homocysteine assay is not sensitive to the presence of iron assay reagents, while the commercial embodiment of the Kawasaki assay is quite sensitive to the presence of iron assay reagents. (*See* YUAN 132 Declaration paragraphs 6-9.) This susceptibility to the "iron assay

interference" compromises the usefulness of the Kawasaki homocysteine assay, as demonstrated by a Warning Letter from the FDA insisting that the manufacturer of that product must take steps to resolve problems attributed to "iron assay interference." Thus the claimed invention provides an unexpected advantage over the Kawasaki assay, especially when the assay is to be used in an instrument that is expected to conduct both a homocysteine assay and an iron assay.

Second, the presently claimed homocysteine assay is not very sensitive to cystathionine levels in the tested samples, while the Kawasaki assay gives very inaccurate results in the presence of cystathionine levels that are known to occur in at least some patients, those with end stage renal disease (*e.g.*, 20 micromolar cystathionine, per the letter from CATCH to its customers). (*See* YUAN 132 Declaration paragraph 10.) This was not expected to be an issue according to CATCH, whose package insert said that cystathionine levels would normally be below about 0.3 micromolar. Yet the package insert has now been revised to recognize that in some cases cystathionine may "cause greater than 20% interference." The presently claimed homocysteine assay, by comparison, is not affected nearly as much by the presence of cystathionine, thus providing a further unexpected advantage for the claimed methods over the Kawasaki assay.

In view of the above, Applicants respectfully request that the rejection be withdrawn.

C. Rejection over Matsuyama et al., Sundrehagen, and Suzuki et al. or Kawasaki et al., and further in view of Yuan (US 6,376,210)

Claims 1-12, 14-16, and 18-21 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Matsuyama et al., Sundrehagen, and Suzuki et al. or Kawasaki et al. as applied to claims 1-8, 10-12, 14-16, and 18-21 above, and further in view of Yuan (US 6,376,210). The Examiner states that Matsuyama et al., Sundrehagen, and Suzuki et al. or Kawasaki et al. render claims 1-8, 10-12, 14-16, and 18-21 obvious; but these references do not expressly disclose an assay for Hcy in every body fluid sample listed in claim 7, and do not disclose that, when the body fluid sample is blood, the blood sample is further separated into a plasma or serum fraction. The Examiner further states that Yuan discloses a method for assaying Hcy in a sample which may be a

body fluid selected from a group consisting of every species listed in claim 7 of the application under examination; and Yuan also discloses further separating blood into a plasma or serum fraction. The Examiner concludes that at the time the invention was made, it would have been obvious to a person of ordinary skill in the art to have tested for Hcy in every type of sample listed in Yuan; and it would have been obvious to have separated a blood sample into a plasma or serum fraction.

As discussed above, rejection to claims 14-16 and 21 is moot in view of cancellation of the claims.

Applicants respectfully traverse the rejection to claims 1-12 and 18-20. Applicants respectfully submit that the cited references do not provide the motivation to combine reference teachings. As discussed above, none of Matsuyama et al., Sundrehagen, Suzuki et al. and Kawasaki et al. teaches or suggests using the two enzymatic reactions that form a cycling reaction system as recited in claims 1-12 or the kits as recited in the claims 18-20; and the Examiner has not established a *prima facie* case of obviousness over claims 1-8, 10-12, and 18-20. The additional reference cited does not cure this deficiency. Yuan does not provide any teachings or suggestions of using the two enzymatic reactions that form a cycling reaction system as recited in claims 1-12 or the kits as recited in the claims 18-20. Thus, Yuan does not provide any additional motivation to combine the reference teachings.

In view of the above, the Examiner has not set forth a *prima facie* case for obviousness. The nonobviousness of the presently claimed homocysteine assay is further supported by the unexpected technical advantages of the presently claimed homocysteine assay over the Kawasaki assay as shown in YUAN 132 Declaration. Applicants respectfully request that the rejection be withdrawn.

D. Rejection over Matsuyama et al., Sundrehagen, and Suzuki et al. or Kawasaki et al., and further in view of Nelson et al. (Lehninger Principles of Biochemistry, 3rd edition, 2000, pages 640-642).

Claims 1-8 and 10-21 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Matsuyama et al., Sundrehagen, and Suzuki et al. or Kawasaki et al. as applied to claims 1-8, 10-12, 14-16, and 18-21 above, and further in view of Nelson et al. (Lehninger Principles of Biochemistry, 3rd edition, 2000, pages 640-642). The Examiner states that as discussed above, Matsuyama et al., Sundrehagen, and Suzuki et al. or Kawasaki et al. render claims 1-8, 10-12, 14-16, and 18-21 obvious; but these references do not expressly disclose producing SAM from ATP and Met by a SAM synthase. The Examiner further states Nelson et al. discloses that methionine adenosyl transferase, also known as S-adenosylmethionine synthase (SAM synthase) in the art, catalyzes the conversion of Met to SAM, where ATP is a co-substrate. The Examiner concludes that at the time the invention was made, it would have been obvious to a person of ordinary skill in the art to have used the reaction described by Nelson et al. in order to produce SAM for the reaction catalyzed by SAM-dependent homocysteine S-methyltransferase.

As discussed above, rejection to claims 14-16 and 21 is moot in view of cancellation of the claims.

Applicants respectfully traverse the rejection to claims 1-8, 10-13, and 18-20. Applicants respectfully submit that the cited references do not provide the motivation to combine reference teachings. As discussed above, none of Matsuyama et al., Sundrehagen, Suzuki et al. and Kawasaki et al. teaches or suggests using the two enzymatic reactions that form a cycling reaction system as recited in claims 1-12 or the kits as recited in the claims 18-20; and the Examiner has not established *prima facie* obviousness over claims 1-8, 10-12, and 18-20. The additional reference cited does not cure this deficiency. Nelson et al. do not provide any teachings or suggestions of using the two enzymatic reactions that form a cycling reaction system as recited in claims 1-8 and 10-13, or the kits as recited in the claims 18-20. Thus, Nelson et al. do not provide any additional motivation to combine the reference teachings.

In view of the above, the Examiner has not set forth a *prima facie* case for obviousness. The nonobviousness of the presently claimed homocysteine assay is further supported by the unexpected technical advantages of the presently claimed homocysteine assay over the Kawasaki

assay as shown in YUAN 132 Declaration. Applicants respectfully request that the rejection be withdrawn.

E. Rejection over Yuan (U.S. Pat. 6,610,504) in view of Shapiro (Methods Enzymol. 1971. 17(Pt. B): 400-405)

Claims 14-16 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Yuan (U.S. Pat. 6,610,504) in view of Shapiro (Methods Enzymol. 1971. 17(Pt. B): 400-405).

Applicants respectfully note that claims 14-16 have been canceled. Accordingly, this rejection is moot. Applicants respectfully request that the rejection be withdrawn.

F. Rejection over Yuan (US 6,610,504) and Shapiro, and further in view of Nelson et al.

Claims 14-17 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Yuan and Shapiro as applied to claims 14-16 above, and further in view of Nelson et al.

Applicants respectfully note that claims 14-17 have been canceled. Accordingly, this rejection is moot. Applicants respectfully request that the rejection be withdrawn.

G. Rejection over Chagoya de Sanchez et al. (Int. J. Biochem. 1991. 23(12): 1439-1443) in view of Kuchino et al. (Cancer Research. 1977.37: 206-208)

Claims 18-20 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Chagoya de Sanchez et al. (Int. J. Biochem. 1991. 23(12): 1439-1443) in view of Kuchino et al. (Cancer Research. 1977.37: 206-208). The Examiner states that Chagoya et al. disclose that SAM, SAH hydrolase, adenosine kinase, and adenosine deaminase are present in rat liver, and the rat liver is a kit comprising SAM, SAH hydrolase, adenosine kinase, and adenosine deaminase. The Examiner further states that Chagoya et al. do not expressly disclose a kit comprising SAM-dependent homocysteine S-methyltransferase. The Examiner states that Kuchino et al. disclose that S-adenosylmethionine homocysteine methyltransferase, also known as SAM-dependent

homocysteine S-methyltransferase, is in rat liver, and the rat liver is a kit comprising SAM-dependent homocysteine S-methyltransferase. The Examiner concludes that at the time the invention was made, it would have been obvious to a person of ordinary skill in the art to have concluded that the rat liver would have served as a kit comprising SAM, SAH hydrolase, adenosine kinase, adenosine deaminase, and SAM-dependent homocysteine S-methyltransferase; and additionally, it would have been obvious to have assayed Hcy in a rat liver sample.

Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, the references when combined must teach or suggest all the claim limitations. Applicants respectfully note that a rat liver is not a kit understood by one skilled in the art. The term "kit" recited in claims 18-20 does not include a naturally occurring tissue or organ; but contains a collection of reagents including SAM-dependent homocysteine S-methyltransferase; SAM, or ATP, Met, and a SAM synthase; SAH hydrolase; and a reagent for assessing Ado (*e.g.*, an adenosine kinase or an adenosine deaminase) to be used for assaying Hcy in a sample. Since neither Chagoya et al. nor Kuchino et al. teach or suggest a kit for assaying Hcy in a sample as recited in claims 18-20, these references, even if combined, do not teach or suggest all the claim limitations.

Moreover, the rat liver is not analogous art to a kit for assaying Hcy in a sample, any more than the whole rat would be: one in search of means to assay for homocysteine would not have any reason to consider using a rat liver, and would obviously have no guidance about how to 'modify' a liver to perform that function. On these grounds, the obviousness rejection may be properly withdrawn.

Further, new claims 24 and 25 recite that "at least one of the S-adenosylmethionine (SAM)- dependent homocysteine S-methyltransferase, S-adenosylmethionine (SAM), ATP, Met, the SAM synthase, the SAH hydrolase, and/o the reagent for assessing adenosine (Ado) is packaged in a container" and the container can be a glass or plastic container. These claimed kits are further differentiated from a rat liver.

In view of the above, the Examiner has not set forth a *prima facie* case of obviousness for claims 18-20. Applicants respectfully request that the rejection be withdrawn.

In view of the above, Applicants respectfully request that the rejections under 35 U.S.C. §103 be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 466992001400. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: November 3, 2005

Respectfully submitted,

By_____

Peng Chen
Registration No.: 43,543
MORRISON & FOERSTER LLP
12351 High Bluff Drive
Suite 100
San Diego, California 92130-2332
(858) 720-5117